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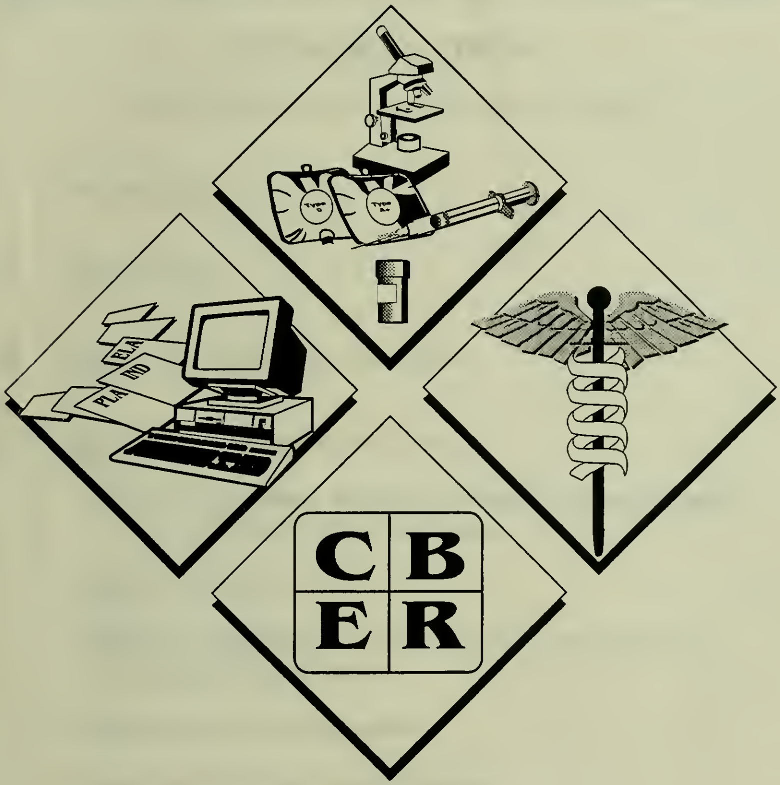

Center for Biologics Evaluation & Research

ANNUAL REPORT FY 95

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1995

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

FY 95 ANNUAL REPORT

(Covering the Period October 1, 1994 through September 30, 1995)

Section I Executive Summary 1

Section II Mission Statement 2

Section III Strategic Plan - CBER 2004 Vision; Goals 3

Section IV Significant Accomplishments For FY 95 4

- Total Biological Actions - Biological Licensing Activities; Biological Investigational New Drug Applications 4
- Significant Approvals 5
- Scientific Accomplishments - including Facility For Biotechnology Resources; Special Interest 10
- Other Regulatory Accomplishments 14
- Prescription Drug User Fee Act Highlights 15
- Reinventing Government 16
- Policy Developments 17
- International Harmonization 18
- Information Management Highlights - including SMART 19
- Management Accomplishments 23
- Organizational Changes 26

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NIH LIBRARY
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Section V Program Descriptions 32

- Pre-Market 32
- Post Market 32
- Science 33
- International Harmonization 35
- Information Management Systems 36
- Organization and Management 36
- People, Facilities and Equipment 37

Section VI Resources 39

Appendix 41

Meetings, Workshops & Seminars
Adverse Events
CBER First Action Performance for Applications
Application Data Summary
Total CBER Submissions Received

EXECUTIVE SUMMARY

The Center for Biologics Evaluation and Research (CBER) is responsible for ensuring the safety, efficacy, potency and purity of biological and related products intended for use in the treatment, prevention or cure of diseases in humans as well as the safety of the nation's supply of blood and blood products. The primary responsibility of CBER is to review the safety and efficacy of vaccines, blood products, certain diagnostic products and other biological and biotechnology-derived human products. CBER's activities include:

- evaluating the safety and effectiveness of biological products *before* marketing, and monitoring the preclinical and clinical testing of new biological products;
- licensing biological products and manufacturing establishments, including plasmapheresis centers, blood banks, vaccine and biotechnology manufacturers;
- AIDS program and policy activities, including research on AIDS therapeutic products, diagnostic tests and vaccines;
- research to establish product standards and develop improved testing methods;
- compliance, lot release program and post market surveillance;
- PDUFA goals met, new research programs, new regulatory initiatives (managed review process for all products).

MISSION STATEMENT

The mission of CBER is to protect and enhance the public health through regulation of biological and related products including blood and diagnostics, vaccines, and biological therapeutics according to statutory authorities. The regulation of these products is founded on science and law to ensure their purity, potency, safety, efficacy and availability.

In fulfilling our mission as a Center of the FDA, we apply the following principles with the highest ethical standards and integrity:

- We develop, maintain, and support a high quality and diverse work force;
- We ensure compliance with laws and regulations through review, education, surveillance, and enforcement;
- We conduct research as an essential element of science-based decision-making;
- We are proactive and encourage innovation, cooperation and collaboration.

STRATEGIC PLAN

CBER VISION: 2004

CBER advances the public health and merits the public trust through innovative regulation to ensure that safe and effective products reach the public as rapidly as possible. CBER demonstrates international leadership in science-based regulation through a managed regulatory process, coordinated research and the use of partnerships.

To that end:

- We will have implemented a managed and integrated regulatory process from discovery to post-marketing;
- Our research will serve as a critical public health resource which is linked to clinical and technical evaluation of traditional and novel products.

CBER's regulatory mission will be our guiding principle.

GOALS

To achieve CBER's vision for the future the following decision-making goals were identified. These goals will be the guiding force in CBER decision-making during the next ten years. While it may be necessary to re-examine the goals in the context of changing forces, we believe that by working towards these goals CBER will continue to be a strong and effective science-based regulatory organization.

- A managed and integrated regulatory process which is seamless from discovery through post-marketing;
- A high quality research program which contributes directly to the regulatory mission;
- A high quality and diverse work force;
- Interactive information systems are integral to all CBER activities;
- Leveraged resources.

SIGNIFICANT ACCOMPLISHMENTS FOR FY 95

TOTAL BIOLOGICAL ACTIONS

There were 2,744 total actions taken on biological and related products. CBER completed 1,430 approval actions in FY 95 of which fourteen were for important new biologic licenses. These included the approval of 4 vaccines, 1 therapeutic, 1 blood product (orphan designation - new treatment) 2 testing devices/kits (new indications), 5 supplements and 1 PMA application. *See Appendix for Application Data Summary.*

The 1,430 approval actions were comprised of 60 PLA and ELA license applications, 1,317 PLA and ELA supplements, 52 NDA supplements, and 1 PMA.

The remainder of the actions (1,314) included approvable and not approvable actions, license revocations (48), withdrawals, refuse-to-file actions, inactivations, and a denial.

BIOLOGICAL LICENSING ACTIVITIES

	FY 93	*FY 94*	*FY 95*
PRODUCTS			
Applications received	41	33	52
Applications approved	31	24	42
Supplements completed *1/*	638	672	1,004
ESTABLISHMENTS			
Applications received	11	14	22
Applications approved	9	10	18
Supplements completed *1/*	267	285	439

(Two licenses are necessary to manufacture and distribute a biological product. One license is for the product and the other is for the establishment in which it is produced. Supplements to licenses are required for any significant change.)

1/Includes approved, withdrawn, inactivated, or denied or refused to file supplements.

Note: The above table only includes licensing submissions. It does not include NDAs, PMAs or 510(k) submissions regulated by CBER.

BIOLOGICAL INVESTIGATIONAL NEW DRUG APPLICATIONS

	FY 93	*FY 94*	*FY 95*
Commercial	224	276	244
Research	303	227	292
Originals received *2/*	527	503	536
Amendments received and reviewed	8,100	9,239	9,882
Total Active INDs *3/*	2,969	2,752	2,802

2/ Includes INDs, IDEs, Master Files and license master files.
3/ Active investigational new drug (IND) applications are those that have not been inactivated, withdrawn, or closed by the sponsor; or inactivated, canceled, transferred or terminated by CBER. Studies may or may not be ongoing under active INDs.

SIGNIFICANT APPROVALS - HIGHLIGHTS

On October 5, 1994, Plague Vaccine for the prevention of bubonic plague was approved. Bubonic plague is transmitted by the bite of fleas infected with *Yersinia pestis*. The new whole-cell vaccine will be used primarily to protect military personnel serving in countries where the disease is endemic. The vaccine is also indicated for people whose occupation frequently puts them at risk of plague disease, usually from contact with infected wild or domestic animals. Sylvatic (wild animal) plague occurs in some parts of the United States.

On November 28, 1994, a new vaccine, Typhoid Vi Polysaccharide Vaccine, was approved; it is used against typhoid fever in adults and children. Typhoid fever is a serious disease which can occur after ingestion of food or water contaminated with *Salmonella typhi*. The new vaccine, which is composed of purified Vi capsular polysaccharide, is indicated for travelers to countries where typhoid fever is endemic. The immunization consists of a single injection of vaccine and may be given to children as young as 2 years old.

On December 22, 1994, Abciximab, a monoclonal antibody to be used in conjunction with angioplasty procedures, was approved. This product can help prevent complications that occur in some angioplasty patients when blood clots cause abrupt closure of the treated coronary artery. When injected, Abciximab binds to platelets and helps prevent them from forming the clots. The multicenter clinical trial with more than 2,000 high-risk coronary angioplasty patients indicated that although Abciximab did not

affect patients' survival, it reduced the incidence of heart attacks and the need for emergency procedure and emergency coronary surgery in surviving patients.

On December 23, 1994, OraSure HIV-1 Oral Specimen Collection Device made by Epitope, Incorporated, was approved. This device is for use in collecting oral fluid samples for the purpose of testing for the presence of Human Immunodeficiency Virus Type 1 (HIV-1) antibodies. The device is a prescription device and is subject to post-market surveillance. In conjunction with this approval, Oral Fluid Vironostika HIV-1 Microelisa System by Organon Teknika Corporation was approved. This assay is intended for the qualitative determination of antibody to HIV-1 only with oral fluid samples obtained using the OraSure HIV-1 Oral Specimen Collection Device.

On February 22, 1995, Hepatitis A Vaccine, the first available for the prevention of hepatitis A in adults and children, was approved. Hepatitis A is a highly contagious viral disease that infects an estimated 150,000 Americans annually. It is generally spread by contaminated food or water, or by close personal contact with an infected person. The disease can also be contracted by consuming raw or undercooked shellfish harvested from contaminated waters. Outbreaks of hepatitis A sometimes occur in institutional settings, including day care centers and facilities that house intellectually impaired children and adults. Military personnel living in field conditions, crowded barracks, and high-risk geographic areas are at higher risk for the disease. Hepatitis A is especially prevalent in developing countries that have poor sanitary systems and standards of hygiene. The vaccine is indicated for international travelers, people living in or relocating to areas where the disease is endemic, some military personnel, and certain high-risk individuals (i.e., some hospital and laboratory personnel).

The chickenpox vaccine, Varivax (Varicella Virus Vaccine Live), was approved on March 17, 1995. An estimated 3.7 million Americans are affected by highly contagious chickenpox each year, with more than 90 percent of the cases occurring in persons under 15 years of age. It is estimated that about 9,300 related hospitalizations and 50 to 10 related deaths occur annually, most of them among young children. Chickenpox is transmitted from a contagious person to others through fluid from broken blisters as well as by coughing or sneezing. The incubation period of the illness is 10 to 21 days. A person is contagious from 1 or 2 days

before the rash appears until all the lesions are dried, usually 4 to 5 days. A single injection of the vaccine is recommended for children ages 12 months to 12 years, while two injections 4 to 8 weeks apart are recommended for those ages 13 and older who have not contracted chickenpox. The vaccine has been shown to be safe and effective when administered at the same time as the measles, mumps, and rubella vaccines.

On March 24, 1995, Rho(D) Immune Globulin Intravenous (Human) was approved. This is the first Rho(D) Immune Globulin for intravenous use. It is the first human blood product of any kind approved for both intravenous and intramuscular use. It was approved for treatment of immune thrombocytopenic purpura (ITP) in Rh-positive patients - a unique application requiring much less globulin administration than other products with this indication. This product is indicated for use in Rh-negative pregnant women with a Rh-positive fetus to prevent development of anti-Rh antibodies in women. Such antibodies can harm subsequent Rh-positive fetuses (erythroblastosis fetalis, “blue baby syndrome”).

SIGNIFICANT APPROVALS

Product Name (Generic Name)	*Manufacturer*	*Indications/Use*
NEW PRODUCTS		
Plague Vaccine	Greer Laboratories, Inc. Lenoir, NC	Plague immunization
Typhoid Vi Polysaccharide Vaccine	Pasteur Merieux Serums et Vaccins, S. A. Lyons, France	Typhoid immunization
Abciximab	Centocor B. V. Leiden, Netherlands	Adjunct to PTCA to prevent acute cardiac ischemic complications in patients at high risk for abrupt closure of the treated vessel
HIV-1 Oral Specimen Collection Device	Epitope, Inc. Beaverton, OR	Oral fluid collection for HIV-1 antibody testing
Hepatitis A Vaccine	SmithKline Beecham Biologicals Rixensart, Belgium	Hepatitis A immunization
Varicella Virus Vaccine Live	Merck & Co., Inc. West Point, PA	New indication for use in individuals 12 months & older
Rho(D) Immune Globulin Intravenous (Human)	Rh Pharmaceuticals, Inc. Winnipeg, Canada	Prevention of Rh sensitization postpartum, after fetomaternal bleed. After mismatched blood or RBC transfusion. Treatment of acute/chronic ITP, ITP secondary to HIV infections

SUPPLEMENTS

Hepatitis B Vaccine (Recombinant)	SmithKline Beecham Biologicals Rixensart, Belgium	Alternative dosage form
Allergen Patch Test	Kabi Pharmacia Service A/S Hillerod, Denmark	New allergen panels
Filgrastim	Amgen, Inc. Thousand Oaks, CA	Treatment of severe chronic neutropenia
Human Immuno-deficiency Virus Type 1	Organon Teknika Corporation Durham, NC	Testing of oral specimens
Red Blood Cells Irradiated	Mississippi Valley Regional Blood Center Davenport, IA	Manufacture of Red Blood Cells Irradiated
Alteplase	Genentech, Inc. S. San Francisco, CA	Accelerated infusion rate
Sargramostim	Immunex Corporation Seattle, WA	Indication for use following induction chemotherapy in older adult patients with acute myelogenous leukemia

SCIENTIFIC ACCOMPLISHMENTS

Major accomplishments in the applied/regulatory research arena include:

- Molecular Biological Assay (MAPREC) for Neurovirulent Revertants in Oral Poliovirus Vaccine (OPV) - a collaborative study with WHO - CBER personnel presented findings, manuals and data worksheets at WHO meeting. CBER use of MAPREC testing of OPV monopools submitted for release is in place for all three types of OPV.
- Herpes viruses establish latency and can be reactivated to produce an acute viral disease identical to that observed in primary infections. The mechanism by which latency is established and reactivation occurs has been investigated at the molecular level. A viral-specific latency associated transcript has been identified which is critical for viral reactivation. Deletion of the gene encoding this transcript attenuates the virus, eliminates the ability of the virus to reactivate but does not alter the ability of the virus to establish or maintain latency.
- Standardization and use of influenza virus vaccines. A high-yield reassortant influenza virus for the new H3N2 virus component of the influenza virus vaccine was produced and may be used as a master seed for the manufacture of vaccine. Molecular techniques developed to identify the origin of each of the eight gene segments in the influenza reassortant viruses are being used to identify and characterize genes in viruses used in vaccine manufacture.
- Development of a quantitative viral capture assay for detection and quantification of HIV RNA in body fluids and culture supernatants.
- Standardization of a multiplex assay for detection of human retroviruses.
- A transgenic model for evaluation of the effects of adhesion/costimulatory molecules in T cell activation was developed. This will aid tremendously in evaluating an important new class of biologicals.

- Lot release testing of HCV RNA on all immunoglobulin products that have not undergone one or more validated viral inactivation or removal steps. CBER developed, and made available to manufacturers, a detailed protocol describing the procedures for RNA extraction and subsequent detection of HCV RNA by RT-PCR in intravenous and intramuscular immunoglobulin products. The protocol converts a PCR method for HCV RNA, to routine analysis of immune globulins submitted for lot release.

- Studies in angiogenesis have led to new model systems for evaluation of angiogenesis, and important new target for biologicals intended to treat malignancies.

- Development of immunotoxin (IL-4 pseudomonas exotoxin) with increased potency.

- A unique latex allergen was isolated, characterized and gene cloned. Two disease resistant proteins have been identified as major apple allergens.

Investigations continue in the areas of HIV, Hepatitis A & C, herpes, etc.

FACILITY FOR BIOTECHNOLOGY RESOURCES

The CBER Facility for Biotechnology Resources (FBR) began operation in FY 95 and reports to the CBER Associate Director for Research in the Office of the Center Director. This core facility is accessible to all CBER scientists. The instrumentation and expertise in protein/peptide, nucleic acid and mass spectrometry technologies have been centralized in this facility. The mission of the FBR is to make existing scientific resources available to all CBER scientists by (a) ensuring access to highly sophisticated, state-of-the-art instrumentation and established scientific expertise; and (b) providing an open forum for information, consultation and discussion through publication of the FBR handbook, seminars, users' group meetings and other means of telecommunications.

The implementation of the core facility operation in CBER results in more efficient utilization of expertise, equipment and chemicals in the conduct of our regulatory program through the procurement, operation and support of the highly sophisticated instrumentation

which provide specific, sensitive and reliable biochemical syntheses and analyses and which represent indispensable tools for accurate characterization of biological/biotechnological molecules represent a major investment in resources - both human and instrumentation. By centralizing scientific expertise and expensive instrumentation into a core facility, costly and unnecessary duplication of resources and effort are averted, thus allowing scientists and support staff additional time to efficiently and expeditiously conduct their regulatory duties and to enhance their productivity. More efficient utilization of chemicals or instruments which are used at full capacity in this facility, compared to those left on idle instruments, results in substantial savings in overall operating cost for the Center. Finally, the core facility is well-equipped to support procedures aimed at evaluating and validating methods used by biotechnology companies for the purification and characterization of biological molecules including those identified as "Well Characterized Products."

The FBR was operational on August, 1, 1995, and in the first five months of operation over 1,300 requests for services were processed.

SPECIAL INTEREST

To facilitate the evaluation of proposed human gene transfer protocols, FDA/CBER and NIH have implemented a consolidated process by which each agency will independently evaluate the clinical use proposals to determine whether they should be reviewed by the Recombinant DNA [deoxyribonucleic acid] Advisory Committee (RAC). Previously, all such proposals were administratively cleared by the NIH Office of Recombinant DNA Activities and reviewed by the RAC as required by the *NIH Guidelines for Research Involving Recombinant DNA Molecules*. "Appendix M," *Points to Consider in the Design and Submission of Protocols for Transfer of Recombinant DNA into the Genome of Human Subjects*. The recently revised guidelines describe the new process by which investigators must simultaneously submit information in a specified format to FDA/CBER and NIH. Both agencies have 15 days to review the protocols and make their determinations. If both agencies concur, proposals using sufficiently established technology may bypass review by the full RAC. These procedures, which were announced at the end of April, 1995, will allow for more rapid development of this area of gene therapy and give FDA/CBER an earlier look at the proposed

investigations. In addition there is agreement that portions of the NIH submission may serve as part of the subsequent IND submission to FDA/CBER.

The CBER animal care program and facilities were reviewed by the American Association for Accreditation of Laboratory Animal Care (AAALAC) site visitors and were recommended for continued full accreditation. The full accreditation status assures CBER investigators that their animal research will continue to benefit from high quality care and facilities; assures the general public that CBER biomedical research and testing is performed in a humane manner.

The Baboon Bone Marrow Transplantation protocol which was submitted to CBER prompted discussion at the Biological Response Modifiers Advisory Committee meeting held in July, 1995, (see Meetings, Workshops, Seminars). Public health risks (inadvertent cross species transmission of infectious agents, primarily viruses), as well as, the rationale of the protocol were considered. The aim of the protocol was to reconstitute the immune system of a patient with advanced HIV disease, using baboon bone marrow stem cells. The committee voted to allow the protocol to proceed, for this one patient, with the provisions that revisions to the consent form would state the public health risks, the need to stay in the area where the transplant was performed, and the requirement for long term follow-up. The protocol was subsequently approved by CBER.

FDA stated in March, 1994, it's intention to regulate, as devices, software products intended for use in the manufacture of blood and blood components, the release of blood or blood components for transfusion or further manufacturing, and for the maintenance of data used to make decisions regarding the suitability of blood donors. This part of the continuing effort to safeguard the nations's blood supply began in 1988 and 1989 when guidance documents relating to blood establishment computerization were first issued.

Manufacturers have been advised to submit a premarket notification for each blood bank software product (device) not in commercial distribution prior to May 28, 1976. In February, 1995, a letter was issued to blood establishment computer software manufacturers further describing requirements and extending the premarket notification filing deadline to March 31, 1996. Premarket notifications began to be filed in August, 1995, and are currently under review.

OTHER REGULATORY ACCOMPLISHMENTS

Regulatory actions support the broad goals of safeguarding the public health and ensuring honesty and fair dealing between regulated industry, FDA/CBER and consumers.

Enforcement Actions: 3 suspensions; 3 notices of intent to revoke; 1 revocation; 25 warning letters; 4 Orders of Destruction/Recall (tissues); 3 seizures were reviewed, but none performed; 648 recalls; 113 inspections; 1 application integrity policies review; 5 letters issued to American Red Cross pursuant to Section VI.A of consent decree; continued American Red Cross oversight and monitoring; 1 debarment.

Bioresearch Monitoring/Regulations: 125 field assignments coordinated and evaluated; 26 *Federal Register* publications.

CBER's Final Rule for post-market reporting of adverse events associated with biological therapeutics and vaccines and a more detailed Guideline was published and took effect this year. Discussion of the new regulation was presented to industry via a teleconference co-sponsored by the Food, Drug and Law Institute.

During the first quarter FY 95, the American Red Cross (ARC), in conjunction with Baxter Healthcare Corporation, Miles Incorporated, and Sandoz Pharmaceutical Corporation, conducted a voluntary market withdrawal of certain blood and plasma products. The market withdrawal was initiated because a frequent ARC blood donor had been clinically diagnosed with Creutzfeldt-Jakob disease (CJD), a rare, usually fatal, degenerative disease of the central nervous system. The market withdrawal included quarantining all undistributed blood products that had been processed from the donor's blood, and retrieving products that had already been distributed but remained unused. FDA/CBER concurred with the decision to withdraw the products to ensure the continued safety of the blood supply.

The *Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived From Transgenic Animals* was made available in August, 1995. The document is intended to assist manufacturers in the production of safe, pure, potent, and effective therapeutic products for human use that are derived from transgenic animals. A transgenic animal is an animal with an altered genome produced by introduction of DNA through human intervention. The Points to Consider document is also intended to help sponsors assure the quality and consistency of data submitted in connection with IND, product or establishment applications.

PRESCRIPTION DRUG USER FEE ACT HIGHLIGHTS

The Prescription Drug User Fee Act (PDUFA) of 1992 authorizes the FDA to collect user fees related to the process for the review of human drug applications. The fees authorized by PDUFA are to be dedicated toward expediting the review of human drug applications. The PDUFA authorizes FDA to collect fees from the prescription drug industry to augment FDA's base resources. These additional resources are to be used to expedite the review process for human drug applications, so that prescription drug products can reach the market more quickly. Excluded products include allergenic extract products; whole blood or a blood component for transfusion; *in vitro* diagnostic biologic products; certain drugs derived from bovine blood; large volume parenterals approved before 9/1/92. Excluded process activities include pre-IND and early IND activities; enforcement policy development; post-approval compliance and surveillance activities, including review of adverse drug reports and annual reports; advertising review activities once marketing of the product has begun; inspections unrelated to the review of covered applications; research unrelated to the human drug review process.

All PLAs, ELAs and PLA/ELA supplements of the overdue backlog were eliminated before the July 2, 1995, goal. Of the 92 submission backlog, fifty-five were inactive and withdrawn by their sponsors, twenty-two were approved, two are classified "approvable" and thirteen are "not approvable". All interim performance milestones have been met. To assure consistency of action a Refuse to File Oversight Committee was established and is in operation. *See Appendix for CBER First Action Performance for Applications.*

REINVENTING GOVERNMENT

CBER's Reinventing Government (REGO) goal was met with the publication:

- *FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products,* which clarifies the establishment requirements related to the use of small scale and pilot scale facilities for the production of biological products. The development of important new biological products is expensive and time consuming. Constructing a new manufacturing facility for a product which has not been fully tested in clinical trials and may fail clinical testing is a major capital expenditure. The most cost effective choice for some companies may be the use of a pilot or small scale facility where the product may be produced at less than full commercial scale. An application for establishment licensure can be made for any facility regardless of the scale of production. The guidance document describes the conditions and procedures for filing such applications and for the subsequent transfer of the product manufacture to a commercial scale manufacturing facility when appropriate.

- Proposed Revision of 21 CFR 601.64, *Prominence of Name of Distributor of Biological Products*, which is proposed to amend the labeling regulations to remove the requirement that the manufacturer's name be more prominent than the distributor and to permit the names of distributors to be prominently displayed on biological product container labels, package labels, and labeling. The proposed change in the labeling requirements is intended to facilitate flexible manufacturing, packaging, distribution, and labeling arrangements, and to harmonize labeling regulations applicable to biologic products and to drug products. The proposed rule is also intended to reduce the regulatory burden on manufacturers who produce both biologics and other drugs. CBER also has performance measures under development. A tissue regulation is in draft form.

- FDA/CBER *Guidance, Changes to Be Reported for Product and Establishment License Applications* was issued and is intended to provide guidance to manufacturers of licensed biological products on changes in manufacturing procedures and establishments that they may implement with and without prior approval by the Director, CBER. This document does not apply to manufacturers of whole blood, blood components, source leukocytes, and source

plasma. It does not address labeling changes. By following this guidance document, manufacturers of licensed biologicals may, in some instances, reduce their reporting burden and facilitate implementation of certain changes.

POLICY DEVELOPMENTS

On August 8, 1995, guidance documents were issued to the blood industry to increase the safety of the U. S. blood supply. Under the new guidance, FDA/CBER recommends that blood establishments begin screening all blood and plasma donors with newer test kits for HIV-1 antigen within three months after FDA/CBER approves one of the kits. Using the antigen tests would reduce by about one week the "window period" between HIV infection and detection. Reducing the "window period" further reduces the chances that HIV-contaminated blood will enter the blood supply and infect recipients of transfused blood or other blood products. Currently, blood donors are screened with tests that detect only HIV antibodies, normally detectable within twenty-two days after infection. The antigen screening tests detect HIV-1 antigens which are the virus's own proteins.

No cases of CJD transmission by any blood or plasma derived products have been reported. The risk of such transmission is considered extremely small. Nevertheless, the possibility of CJD transmission through blood products cannot be ruled out. Therefore, FDA/CBER has recommended that blood establishments should withdraw and quarantine products subsequently found to have come from donations of individuals diagnosed with or at risk of CJD. These quarantined products could be released in the case of blood products shortages if the products bear special labeling noting the CJD risk. FDA/CBER also recommends that blood donors now be questioned to determine if they have risk factors from CJD, and that at-risk individuals be permanently deferred from donating blood.

Recommendations were also issued for the labeling and use of units of whole blood, blood components, source plasma, recovered plasma, or source leukocytes obtained from donors with elevated levels of alanine aminotransferase (ALT). Earlier this year, the Blood Products Advisory Committee concluded that the continuation of ALT testing of whole blood and source plasma donors was not scientifically justified. FDA/CBER does not recommend either for or against ALT testing. However, if a blood

establishment elects to perform the ALT test, units with an ALT level greater than twice the upper limit of the normal range should not be transfused, and should be labeled "ALT Elevated" and "Caution: For Laboratory Research Only."

On July 11, 1995, FDA/CBER announced the availability of: *FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products*. The guidance document for manufacturers of biological products clarifies the licensing requirements for the use of small scale and pilot facilities for the development and manufacture of biological products. This document clearly articulates that pilot facilities are eligible for licensure. The guiding principle is that an application for establishment licensure can be made for any facility which is fully qualified, validated, operated in accordance with current good manufacturing practices (CGMPs), and otherwise complies with applicable law and regulations.

On July 14, 1995, FDA/CBER announced the availability of a guideline intended to assist manufacturers of blood and blood components, including blood banks, blood centers, transfusion services, and plasmapheresis centers in developing quality assurance (QA) programs that are consistent with recognized principles of QA and CGMPs. To ensure the continued safety of the nation's blood supply, it is essential that blood establishments implement effective control over manufacturing processes and systems. FDA/CBER believes that this can be accomplished by each blood establishment developing a well planned, written and managed QA program designed to recognize and prevent the causes of recurrent deficiencies in blood establishment performance. The emphasis of a QA program is on preventing errors rather than detecting them retrospectively.

INTERNATIONAL HARMONIZATION/ ACTIVITIES

CBER actively participates in FDA policy and technical cooperation activities in formal government-to-government relationships. These include bilateral, trilateral and multi-lateral diplomatic activities with Canada, Mexico, the European Union, Japan, Russia and the United Kingdom. CBER staff and laboratories provide expertise and support to numerous international technical bodies including ten WHO committees, five committees/development groups of the Global Program on Vaccines (GPV)/Children's Vaccine Initiative (CVI) and, twelve other international organizations focusing on an array of scientific

issues. Direct technical assistance has been provided to India and Mexico with the funding support of USAID; under the Gore/Chernomyrdin Health Committee and in cooperation with other PHS agencies, CBER has provided technical training and support to Russia in the field of infectious diseases, most notably addressing the Diphtheria epidemic in Russia; and under the auspices of the U.S./Israel Science and Technology Commission has provided in-country training to GCPs.

CBER staff also engage in regulatory/scientific international activities, such as, international inspection of foreign manufacturers when their products fall within CBER's jurisdiction and joint reviews of applications with Canada. CBER staff also routinely provide their time and expertise, at the professional level, by presenting at international scientific meetings, responding to technical inquiries from throughout the world, consulting with international visitors, serving in editorial capacities for international professional journals.

INFORMATION MANAGEMENT HIGHLIGHTS

Projects supporting improvements in the management of the entire life cycle of the review/regulatory process are:

- The Outreach program, the Information Technology (IT) Decision-making Model, the IT Implementation Committee (ITIC) and related working groups are all part of an on-going process to improve communication with and participation by management and users. More technical information and assistance is available to users. Both users and management have an opportunity to provide input to and participate in IT decisions.

- Hardware and software decisions supporting the move towards paper-less applications are being implemented. Industry will be able to choose the most cost effective commercial off-the-shelf software packages to meet their needs for submitting paper-less applications. Hardware supporting greater access for reviewers to share information and interact with review committee members without the need of files being sent from person to person and/or telephone tag.

- The Blood Logging and Tracking (BLT) system will track all documents from the point of mail receipt to Division of Blood Applications (DBA) to final disposition, and will act as the pilot for managed review of all blood activities. The BLT system will permit CBER to move towards better monitoring of blood bank performance, identification of trends and problems in early stages of development, closer interaction with the field staff and more rapid issuance of guidance to the field and industry. BLT is in the pilot test stage with 20 users in the Office of Blood Research and Review.

- CBER developed the application for the Facility for Biotechnology Resources (FBR) which allows all CBER scientists to request a variety of analytical tests electronically. It is a user friendly system that provides reports of statistical data and for workload scheduling in addition to requesting analytical tests.

Further supporting the goal set forth in the CBER Strategic Plan, and the Agency goal to increase the speed of the review process, CBER is:

- enhancing the tracking system for PDUFA-related submissions that produces a monthly performance tracking report which highlights high priority categories, *i.e.*, AIDS and biotechnology;

- establishing recommended software submission standards for industry to submit paper-less applications. Sponsors will be able to choose from a variety of suites of commercial off-the-shelf software packages which are supported by the Center. The packages under consideration have a wide range of functions at a wide variety of costs; sponsors will be able to choose the most cost effective package to meet their needs for submitting paper-less applications;

- establishing a network version of an application on a stand-alone server with bridging capabilities to the CBER VAX for internal communications. The applications will be on CD-ROM loaded to a CBER info server with only the reviewers having access at location specific hardware to

conduct reviews. This will enable a paper-less application with network access for reviewers to share and interact with review committee members.

SUBMISSION MANAGEMENT AND REVIEW TRACKING (SMART)

SMART, an FDA initiative, is designed to reduce the time required to bring new products to market through process improvements and the use of information systems technologies in the preparation, submission, and review of industry applications. SMART, when fully implemented over several years, will enhance communications at all levels and will facilitate electronic information interchange between FDA and industry during the entire product life cycle from IND through post-market surveillance. The CBER SMART pilot programs launched in FY 95 are:

Gene Therapy Information Network (GTIN) - provides CBER improved capabilities to track the results of gene therapy and enabling patient monitoring in clinical trials. The patient monitoring in clinical trials satisfies a congressional mandate for longitudinal follow-up and outcome assessments. Data has been incorporated from NIH's Recombinant DNA Advisory Committee as well as the Cystic Fibrosis Foundation. Benefits include: real-time access to adverse event data, enabling quick modifications to protocols that facilitate reducing costs and avoiding delays in the biologics development cycle; facilitates the exchange of scientific, non-proprietary information between academic institutions and industry; improves PLA reviews by fostering interaction between sponsor researchers and CBER regulators during the IND stage; and improves the ability to keep pace with the exponential growth of data in this novel therapy area.

Computer-Assisted Product License Application (CAPLA) - provides CBER with guidance manual, procedures and tools to receive, track and review data. Benefits include: providing clear guidance to and potential for decreased costs for industry when submitting CAPLAs; increasing the likelihood of consistent electronic submissions; and providing automated tools for reviewing data in CAPLAs. In FY 95, CAPLAs were received from seven different companies for seven different products.

Regulatory Management System (RMS) - RMS is intended to provide CBER with an integrated information system that supports the full range of regulatory functions, from the review of INDs through post-market surveillance. RMS will:

- include an integrated database easily accessible to all users;
- build on the functionality of current systems, as well as, SMART pilots underway and will accommodate new or enhanced capabilities;
- support the broad range of regulatory functions CBER performs, from planning through surveillance, assisting both management and reviewers;
- provide a foundation through an open system, standards-based approach, to easily incorporate new technologies as appropriate.

Lot Release Imaging System (LRIS) - provides CBER with the capability to accept and process lot protocol data electronically, which includes viewing tools and guidance on electronic submission formats to industry regarding product data. Benefits include: reducing time to complete lot protocol reviews; supporting the review of lot protocol data by multiple reviews simultaneously rather than sequentially; potential to increasing the number of manufacturers using electronic submissions; archiving data with minimum physical storage and little or no deterioration. Electronic submissions for lot release was piloted in FY 94 and was fully operational in FY 95.

Establishment Licensing Application (ELA) *System Improvements* - assesses document management and use of *Documentum* (automated workflow software) to assist reviewers in generating and routing internal review documents as well as correspondence with sponsors. Key benefits include: shortening ELA review time; providing on-line access to BRMS tracking system, correspondence and review documents; linking manufacturing issues with an electronic record of response, agreements, and decisions; utilizing imaging tools to analyze blueprints and diagrams.

MANAGEMENT ACCOMPLISHMENTS

CBER is a people-intensive organization. Its ability to achieve its mission is highly dependent on the determination and quality of management leadership and the capabilities and dedication of its people. CBER's performance is also influenced by its management processes, structure, and training opportunities.

RESOURCE REPORTING SYSTEM

Data continued to be collected at the branch level by program category (Blood, Therapeutics, Vaccines, Allergenics) and by major activities (IND review, Product and Establishment license review, Surveillance and Enforcement and Research) by the Basic Workload Measurement (BWM) survey. Through the fourth quarter, all offices reported actual hours spent on activities. An automated collection process was initiated this year and three Offices reported hours on-line in a "paperless" format.

The BWM data is used extensively for PDUFA reporting to provide percentage data by cost center for justification and use of collected funds. The Center was able to acquire additional funding in FY 95 for PDUFA activities due to the BWM data. The Office of Management provided development, implementation and training to automate the data collection process. The automated program increased the speed and accuracy of data retrieval and reporting capabilities and allowed for more efficient resource efforts.

MANAGED REVIEW PROCESS

The Managed Review Process (MRP) is fully implemented. The MRP covers all submissions to CBER - PDUFA and non-PDUFA, original applications and supplements. Milestones include dates set for the administrative processing of a submission; assignment of the review committee; the 45/60 day filing meeting; and the complete actions of the review process. MRP emphasizes good science and coordination of ancillary activities, such as, bioresearch monitoring, advisory committee review, inter- and intra- Center consultations and pre-licensing inspections. The process begins during the IND phase and continues through the life of the product/establishment application/supplement. Offices have instituted monthly applications status discussions among division directors to overview the process.

GOOD REVIEW PRACTICES

CBER reviewers participated with CDER in a series of workshops to develop an action plan that will evolve into the guidelines that will describe Good Review Practices (GRP). Participation in this effort comes from all levels of CBER, encompassing many disciplines. The work continues with the task force groups addressing a variety of issues that will ultimately lead to the creation of Good Review Practices that will be analogous to the good manufacturing practices (GMP) guidelines that FDA prescribes for industry. The GRPs will improve efficiency, quality of reviews and reviewer consistency across the organization. The outcome will be the emergence of a "science of regulatory review" responsive to evolving technologies.

EQUAL EMPLOYMENT OPPORTUNITY (EEO)

The pilot Administrative Detail Program, a short-term developmental program targeted for non-supervisory employees in grades GS-5 through 12, commenced this fiscal year. The program provides 120 day detail opportunities to gain hands-on experience and evaluate participant potential for one of the eight administrative occupations offered. Eight minority employees participated in this year's sessions. The Brown Bag Series of informative workshops covered: Reinvention of Government; Managing Stress; Effective Interviewing Techniques; Career Assessment and Planning; Dealing with Difficult People; Carpal Tunnel Syndrome; and, how to establish Student Internships with Galluadet's Experiential Programs Off Campus. Eight mentors were matched with eleven proteges in the Mentoring Program. Twelve students from Historically Black Colleges and Universities in the Washington, D. C. area completed an intensive cellular and molecular immunology graduate course sponsored by CBER and the Foundation for Advanced Education in the Sciences, Inc. Collaborative projects with NIH Minority Access to Research Careers (MARC) program and NSF Alliances for Minority Participation (AMP) program to sponsor and place research students were established. Two students from these programs worked with CBER scientists for eight weeks.

FACILITIES

Building 29B on the NIH Campus was completed. Laboratory space was prepared and more than 100 scientists moved in. The building is fully occupied. Building 29B is the site of most of the AIDS review research occurring in CBER.

TRAINING AND PROFESSIONAL DEVELOPMENT

In FY 95, Professional Development included:

Reviewer Training
- Core Courses are offered through both video and live presentations. The Core Courses are: Overview of the Regulation of Biologics; Overview of the IND Process; Overview of the PLA and ELA Process; Post-marketing Regulations; Consultation Resources. Four hundred eighteen employees attended the five core courses this year.
- Technical Courses: IND Application Review and Establishment Licensing Issues were offered and trained one hundred sixty-five employees.
- PLA Technical Issues, Module V, has been redeveloped into five new modules: Manufacturing Concerns: Source Materials and Propagation; Manufacturing Concerns: Purification Concerns and Pharmaceutical Finishing; Manufacturing Concerns: Product Characterization; Seminars in Biopharmaceutical Toxicology and Pharmacology; Clinical Trial Design and Analysis for Biopharmaceuticals. Presentation of these courses is expected in FY 96.

New Reviewer Orientation
- The program was redesigned as "learn at your own pace" videotapes with corresponding handbooks. This program meets the expressed needs from reviewers for immediate information on the "how to" as they come on board CBER.

Reviewer Training
- International Conference on Harmonization (ICH) - CBER assumed the lead for the Agency for this training. Four courses: Overview of ICH Guidelines; Safety (Pre-clinical Study Guidelines); Quality; Efficacy (Clinical Study Guidelines). Three hundred thirty employees were trained.

Research Training
- The first seminar on this track, CBER Investigator Orientation: Use of Experimental Animals, developed in conjunction with OELPS, Division of Veterinary Services, was presented to seventy-four employees.

Case Study Seminars
- OELPS: Post Licensure Surveillance of Biological Product Safety
- OTRR: Evaluation of Product Equivalence for Biological Products were presented to 110 employees.

ORGANIZATIONAL CHANGES

In FY 95, the following organizational changes were approved:

In the Office of Establishment Licensing and Product Surveillance (OELPS), Division of Biostatistics and Epidemiology, the Adverse Experience Branch and the Epidemiology Branch were combined into the Epidemiology Branch.

In the OELPS, Division of Product Quality Control, the Laboratory of Biological Testing and the Laboratory of Reference Reagents were combined into the newly created Laboratory of Standards and Testing.

In the Office of Therapeutics Research and Review, the Immunoconjugates Staff was upgraded to the Laboratory of Immunobiology.

In the Office of Therapeutics Research and Review, Division of Clinical Trial Design and Analysis, the Oncology Staff, the General Medicine Staff, the Pharmacology and Toxicology Staff were each upgraded to Branch status. The Immunology and Infectious Disease Branch was established.

In the Immediate Office of the Director the EEO and Minority Recruitment Staff was renamed to the Equal Employment Opportunity Staff.

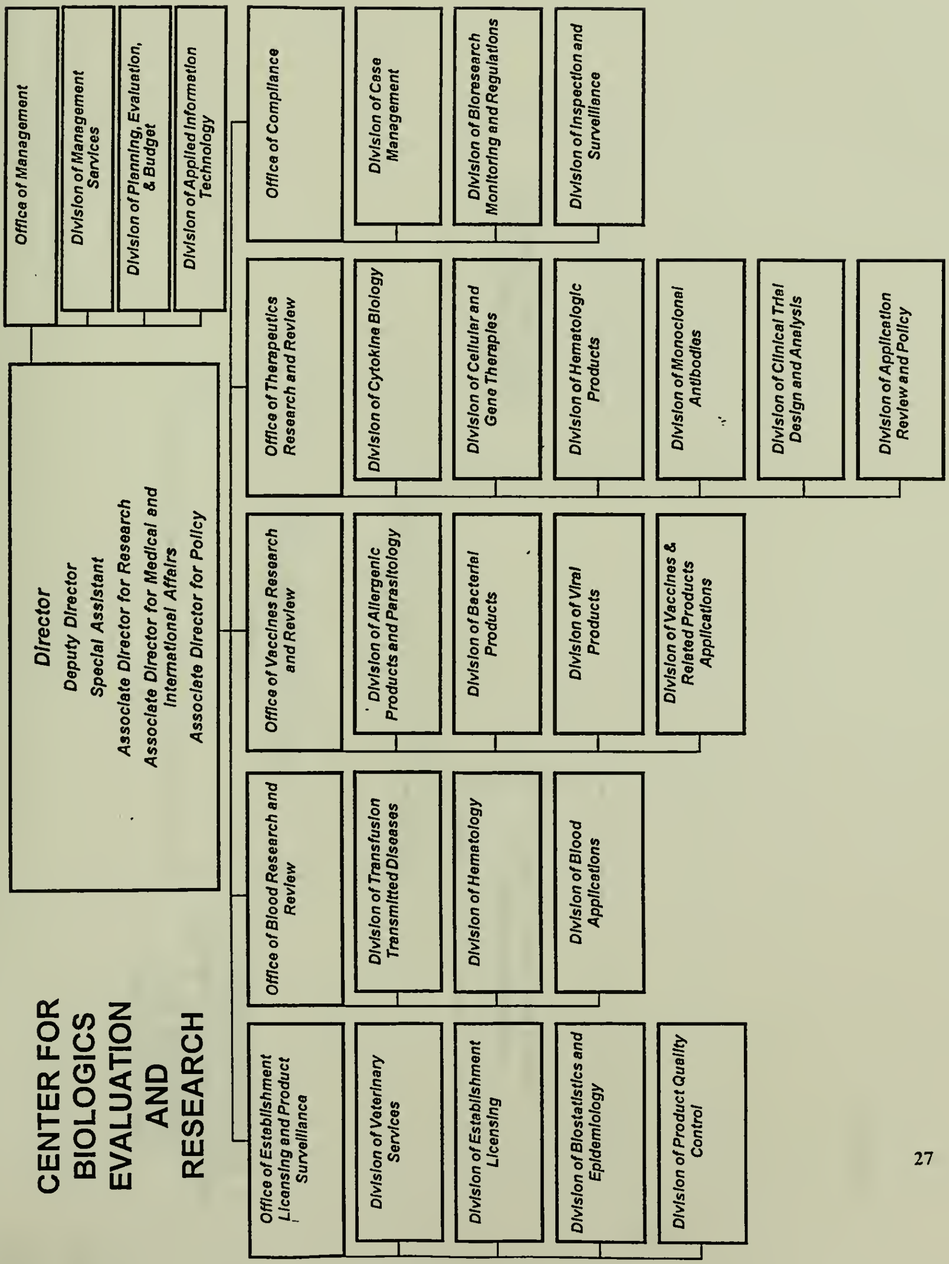
In the Office of Compliance (OC) the Division of Bioresearch Monitoring and Regulations was renamed to the Division of Regulations and Policy. The Branch structure in each of the three OC Divisions was abolished.

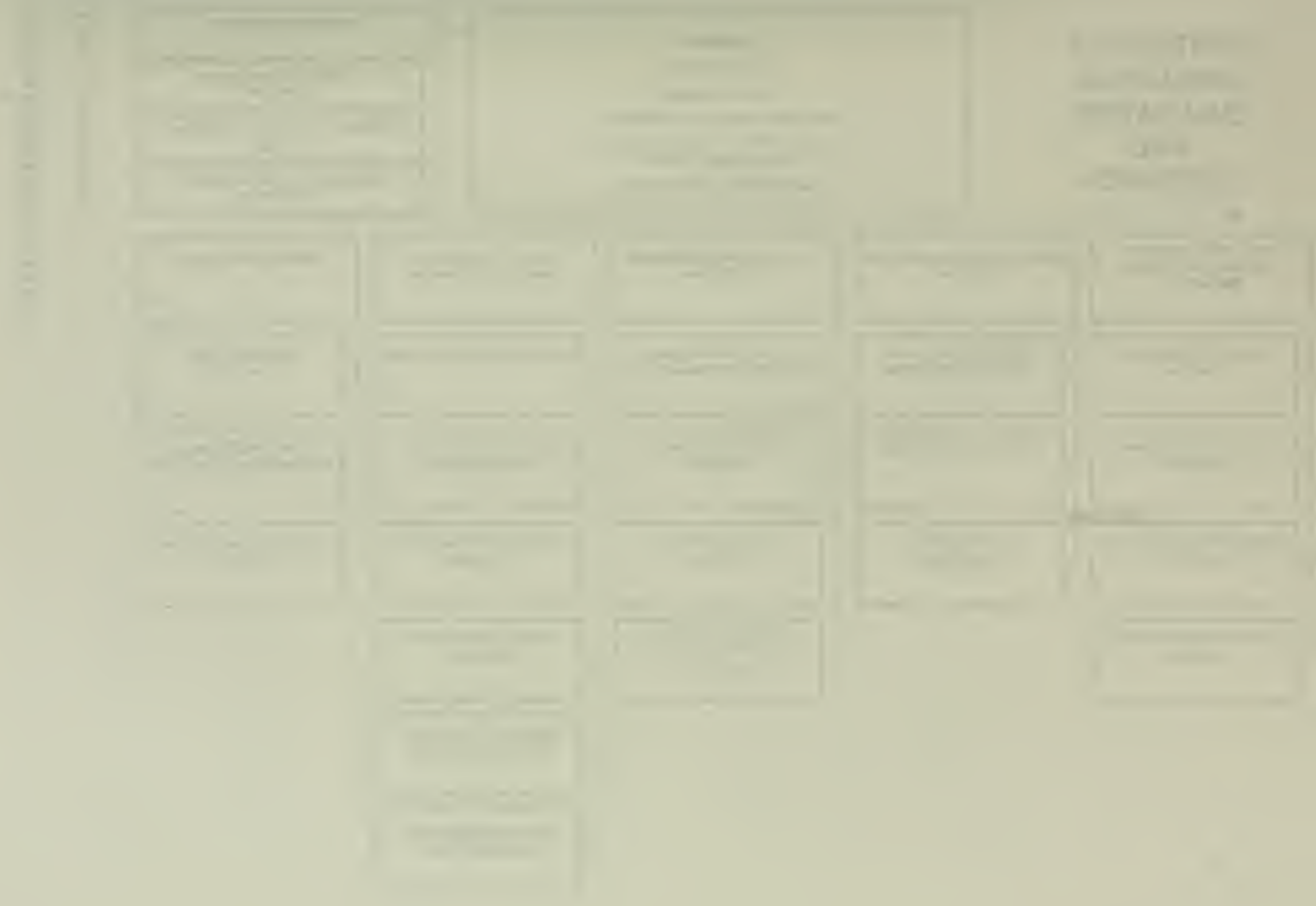
In FY 95, these senior management changes were made:

Frank P. Claunts, Director, Office of Management
James C. Simmons, Director, Office of Compliance
Jay P. Siegel, Director, Office of Therapeutics Research and Review

ORGANIZATION CHART

CBER - END OF FY 95

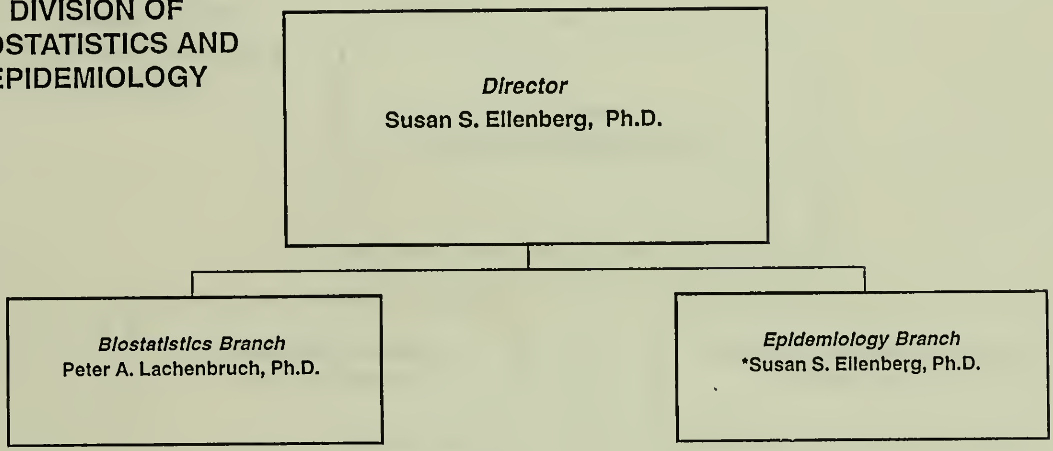

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
Director
Deputy Director
Special Assistant
Associate Director for Research
Associate Director for Medical and International Affairs
Associate Director for Policy
Office of Management
Division of Management Services
Division of Planning, Evaluation, & Budget
Division of Applied Information Technology
Office of Compliance
Division of Case Management
Division of Bioresearch Monitoring and Regulations
Division of Inspection and Surveillance
Office of Therapeutics Research and Review
Division of Cytokine Biology
Division of Cellular and Gene Therapies
Division of Hematologic Products
Division of Monoclonal Antibodies
Division of Clinical Trial Design and Analysis
Division of Application Review and Policy
Office of Vaccines Research and Review
Division of Allergenic Products and Parasitology
Division of Bacterial Products
Division of Viral Products
Division of Vaccines & Related Products Applications
Office of Blood Research and Review
Division of Transfusion Transmitted Diseases
Division of Hematology
Division of Blood Applications
Office of Establishment Licensing and Product Surveillance
Division of Veterinary Services
Division of Establishment Licensing
Division of Biostatistics and Epidemiology
Division of Product Quality Control



ORGANIZATION CHART

REORGANIZED IN FY 95

CBER-OELPS DIVISION OF BIOSTATISTICS AND EPIDEMIOLOGY



Director
Susan S. Ellenberg, Ph.D.

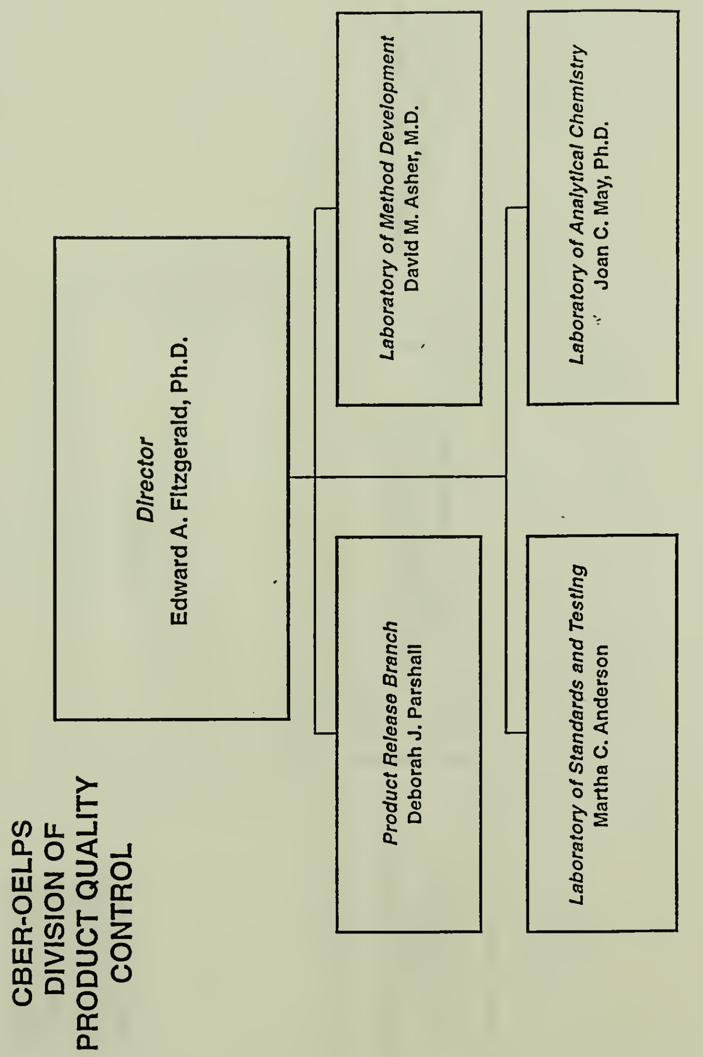
Biostatistics Branch
Peter A. Lachenbruch, Ph.D.

Epidemiology Branch
*Susan S. Ellenberg, Ph.D.

*Acting

ORGANIZATION CHART

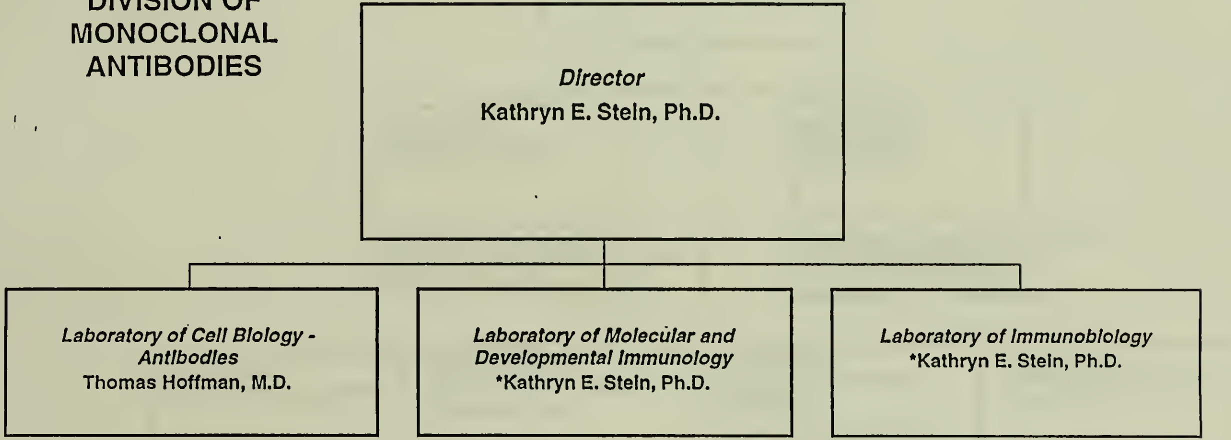
REORGANIZED IN FY 95



ORGANIZATION CHART

REORGANIZED IN FY 95

CBER-OTRR DIVISION OF MONOCLONAL ANTIBODIES



Director
Kathryn E. Stein, Ph.D.

Laboratory of Cell Biology - Antibodies
Thomas Hoffman, M.D.

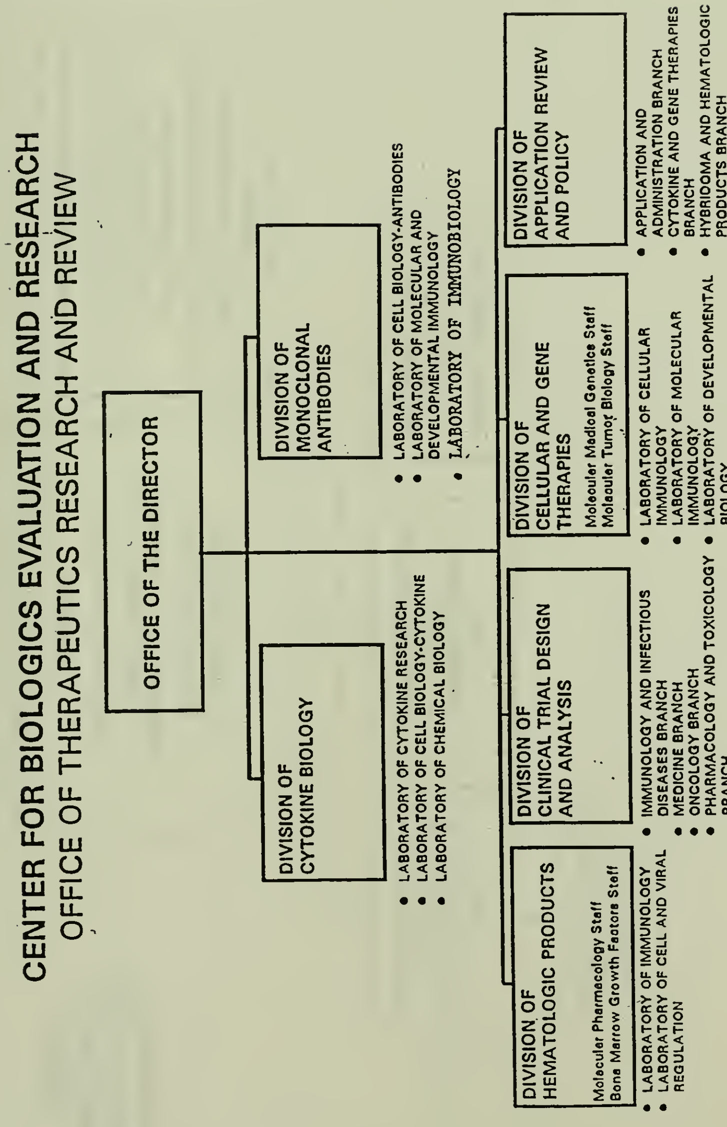
Laboratory of Molecular and Developmental Immunology
*Kathryn E. Stein, Ph.D.

Laboratory of Immunobiology
*Kathryn E. Stein, Ph.D.

*Acting

ORGANIZATION CHART

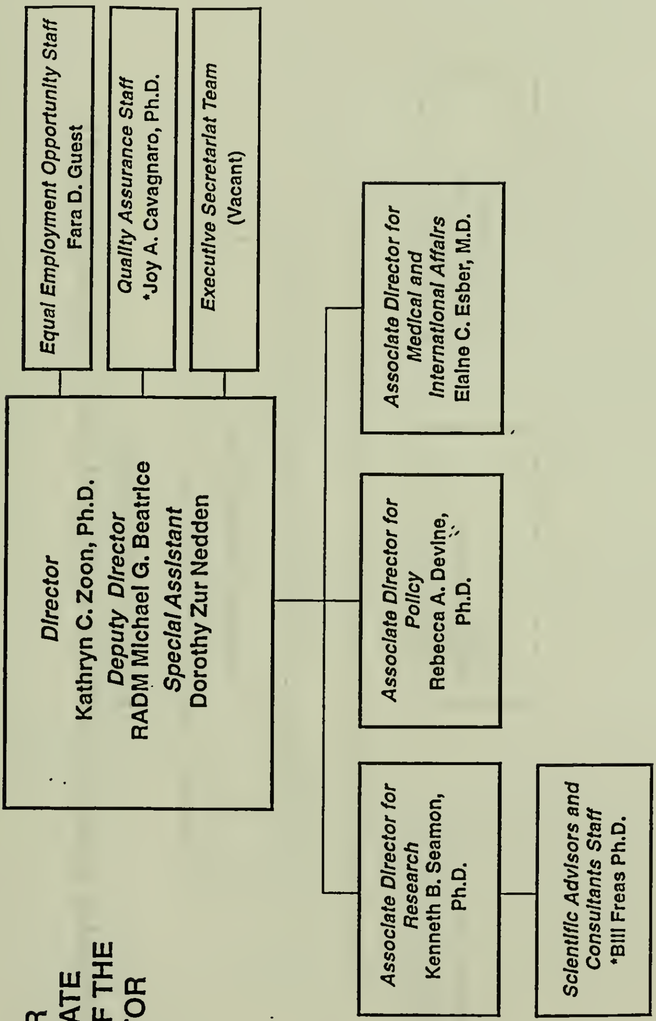
REORGANIZED IN FY 95


CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
OFFICE OF THERAPEUTICS RESEARCH AND REVIEW
OFFICE OF THE DIRECTOR
DIVISION OF CYTOKINE BIOLOGY
• LABORATORY OF CYTOKINE RESEARCH
• LABORATORY OF CELL BIOLOGY-CYTOKINE
• LABORATORY OF CHEMICAL BIOLOGY
DIVISION OF MONOCLONAL ANTIBODIES
• LABORATORY OF CELL BIOLOGY-ANTIBODIES
• LABORATORY OF MOLECULAR AND DEVELOPMENTAL IMMUNOLOGY
• LABORATORY OF IMMUNOBIOLOGY
DIVISION OF HEMATOLOGIC PRODUCTS
Molecular Pharmacology Staff
Bone Marrow Growth Factors Staff
• LABORATORY OF IMMUNOLOGY
• LABORATORY OF CELL AND VIRAL REGULATION
DIVISION OF CLINICAL TRIAL DESIGN AND ANALYSIS
• IMMUNOLOGY AND INFECTIOUS DISEASES BRANCH
• MEDICINE BRANCH
• ONCOLOGY BRANCH
• PHARMACOLOGY AND TOXICOLOGY BRANCH
DIVISION OF CELLULAR AND GENE THERAPIES
Molecular Medical Genetics Staff
Molecular Tumor Biology Staff
• LABORATORY OF CELLULAR IMMUNOLOGY
• LABORATORY OF MOLECULAR IMMUNOLOGY
• LABORATORY OF DEVELOPMENTAL BIOLOGY
DIVISION OF APPLICATION REVIEW AND POLICY
• APPLICATION AND ADMINISTRATION BRANCH
• CYTOKINE AND GENE THERAPIES BRANCH
• HYBRIDOMA AND HEMATOLOGIC PRODUCTS BRANCH

ORGANIZATION CHART

REORGANIZED IN FY 95

CBER IMMEDIATE OFFICE OF THE DIRECTOR



Director
Kathryn C. Zoon, Ph.D.
Deputy Director
RADM Michael G. Beatrice
Special Assistant
Dorothy Zur Nedden

Equal Employment Opportunity Staff
Fara D. Guest

Quality Assurance Staff
*Joy A. Cavagnaro, Ph.D.

Executive Secretariat Team
(Vacant)

Associate Director for Medical and International Affairs
Elaine C. Esber, M.D.

Associate Director for Policy
Rebecca A. Devine, Ph.D.

Associate Director for Research
Kenneth B. Seamon, Ph.D.

Scientific Advisors and Consultants Staff
*Bill Freas Ph.D.

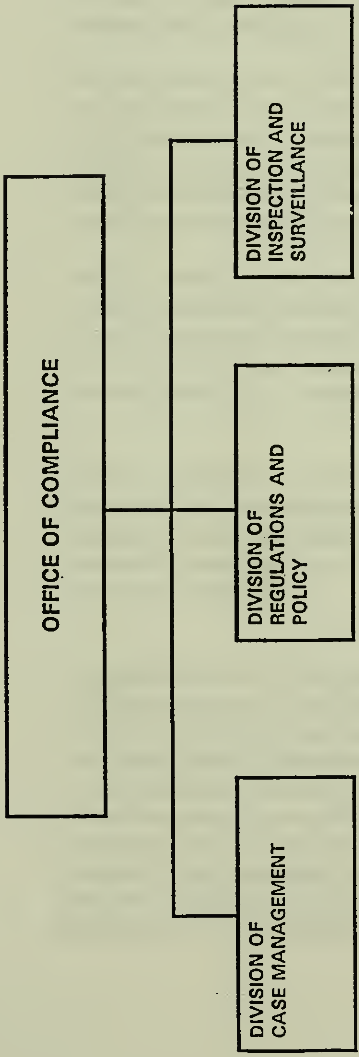
*Acting

ORGANIZATION CHART

REORGANIZED IN FY 95

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

OFFICE OF COMPLIANCE


OFFICE OF COMPLIANCE
DIVISION OF CASE MANAGEMENT
DIVISION OF REGULATIONS AND POLICY
DIVISION OF INSPECTION AND SURVEILLANCE

[illegible]

PROGRAM DESCRIPTIONS

PRE-MARKET

Pre-market review activities are a core component of CBER's mission. CBER is responsible for assuring that biological products - any virus, therapeutic serum (blood & blood products), toxin, antitoxin or analogous product applicable to the prevention, treatment or cure of diseases or injuries of humans - are safe and effective prior to marketing.

In FY 95 CBER received 1,438 PLAs & Supplements, 414 ELAs and Supplements, 10,418 INDs and Amendments, 53 510(k)s and 7,256 lots for release. Despite the size of their workload, CBER regulatory scientists work closely with product sponsors to ensure that the public receives maximum benefit and minimum risk from timely approved biological products.

CBER is continually challenged by the need to regulate new products of increasing technological complexity while still making strides in improving the efficiency and speed of the review process. We have invested in our science base to cope with new and increasing technological complexity.

POST-MARKET

CBER is responsible for providing regulatory oversight for 386 licensed biological manufacturing establishments as well as for regulating the safety and quality of imported products. CBER's post-market responsibilities also include establishment inspections and product surveillance.

ESTABLISHMENT INSPECTIONS

The growing number of biotechnology-based drugs requires highly skilled inspectors due to rapidly changing and complex production processes. In addition, many biotechnology drug sponsors are small firms with limited experience in meeting manufacturing and product standards. Continued concern about the safety of the nation's blood supply and difficulties experienced by the blood industry in complying with good blood banking practices require a concerted effort to modernize blood collection and distribution practices. There is already a major backlog of blood processing problems that have been identified but not resolved.

PRODUCT SURVEILLANCE

The CBER Division of Biostatistics and Epidemiology reviews and investigates the growing post-market reporting of product adverse experiences. CBER monitors the Vaccine Adverse Event Reporting System (VAERS), MEDWatch and hospital fatality reports for biologic related cases.

SCIENCE

CBER is a science-based organization. The knowledge and capabilities of its scientific staff are integral to product review, surveillance and compliance, problem analysis and other responsibilities.

Science underpins CBER's regulatory activities. CBER scientists directly support regulatory decisions by: assessing risks associated with CBER-regulated products, setting standards that minimize risk, testing products against those standards, improving the usefulness and precision of risk assessment methods, and developing methods to increase the accuracy of sample analysis and detection of biological substances. CBER is dependent on science to:

- Provide a sound scientific basis for regulatory decisions.
- Stay current with advancing knowledge and technology.
- Expedite product development.
- Transfer technology.

CBER scientists include toxicologists, microbiologists, molecular biologists, chemists, biochemists, physicians, pharmacologists, engineers, statisticians and professionals in many other disciplines who conduct research applied to specific regulatory issues. In addition to the direct use of CBER research results, research enables our scientists to maintain the in-depth expertise necessary to make sound regulatory decisions.

On August 5, 1995, CBER announced that it established the CBER Facility for Biotechnology Resources (FBR), which is designed to provide state-of-the-art bimolecular technology services to the

CBER scientific staff and to provide information and a forum for consultation for CBER scientists. The facility is equipped with sophisticated instrumentation to support:

- The automated synthesis, purification, and characterization of high-quality peptides and oligonucleotides;
- The preparation and sequence analysis of picomolar amounts of proteins and peptides purified for polyacrylamide gels or by other techniques; and
- The determination of the molecular mass of small peptides and larger protein molecules by mass spectrometry.

The excellence of the CBER scientific team is evident in the 307 technical papers published in many different peer-reviewed scientific journals and the awards received this year:

FDA Scientific Achievement Awards:

Excellence in Laboratory Science - Dennis Klinman, MD, PhD
Michael Norcross, MD, PhD

Excellence in Review Science - Ira J. Berkower, MD, PhD

FDA Outstanding New Investigator of the Year - Philip R. Krause, MD

Recognition for the work of CBER scientists also came from:

Indo-U. S. Vaccine Action Programme - Richard Kenney, MD

NIH Intramural AIDS Targeted Antiviral Program - Basil Golding, MD; Andrew Dayton, MD, PhD

Women's Health Program - Basil Golding, MD

INTERNATIONAL HARMONIZATION

CBER engages in activities directed toward international harmonization of regulatory requirements to assure conformance with sound scientific standards, to safeguard U. S. public health, to facilitate the availability of safe and effective products worldwide, and to support efficiencies in product development.

The process of international harmonization encompasses bilateral and multilateral actions taken by the regulatory authorities of the world to achieve common or compatible approaches to regulation. CBER participates in dozens of separate international activities each year, including many international forums.

International harmonization activities include the following areas: 1) Development of international standards, 2) Development of trade policy and free trade agreements, 3) Enforcement, 4) Technical assistance, and 5) Education and information sharing.

CBER has been an active participant and effective leader in international activities by lending invaluable technical assistance to others, negotiating agreements, and helping to develop international product standards vital to FDA's mission.

In addition to CBER's participation in developing ISO standards for medical devices and on WHO committees developing international standards for biologicals, CBER is involved in a major effort to harmonize the technical requirements for new biologics among the European Union (EU), Japan, and the United States, through participation in meetings of the International Conference on Harmonization (ICH).

The ICH is an effort between regulatory authorities and the pharmaceutical industry to identify areas where changes in requirements, harmonization in the interpretation and application of guidelines, or greater mutual acceptance of research and development procedures could facilitate product approval and lead to a more economical use of human, animal and material resources without compromising safety.

INFORMATION MANAGEMENT SYSTEMS

The CBER Office of Management through the Division of Scientific and Management Information Systems (DSMIS) designs, implements and monitors information systems for the Center. It provides support services to the Center scientific and management micro-computer user community in the form of consultation, documentation of procedures, resolving hardware and software related problems, and providing custom training and education. Assistance/consultation is provided to support the acquisition of state-of-the-art equipment and technology for the Center. DSMIS establishes and monitors the implementation of Agency standards and policies for all automated data processing activities.

DSMIS is the Center contact with the Agency's ADP operations. DSMIS is responsible for development, implementation and maintenance of systems to receive the submission of electronic product applications. The Division participates as a member of the Information Management Council (IMC); through a collaborative effort it provides information strategy input and technical expertise and implements the goals and objectives outlined by the IMC.

ORGANIZATION AND MANAGEMENT

The CBER Office of Management monitors the development and operation of planning systems for Center activities and resource allocations and advises the Center Director on Center administrative policies and guidelines and information systems and services. The Office directs and counsels Center managers through program evaluation and technological forecasting and plans and directs Center operations for financial, personnel management and administrative management services. The Office directs Center organization, management and information systems, manages studies designed to improve processes and resource allocations in the Center, and advises the Center management on contract and grant proposals.

PEOPLE, FACILITIES AND EQUIPMENT

The Recruitment Staff initiatives include interviewing and/or speaking at scientific societies and pharmaceutical companies. Other initiatives include the placement of ads in major scientific journals and on electronic media such as the NIH Ednet and the Internet. CBER Recruitment also has joint recruitment initiatives with CDER Recruitment which allow for the sharing of resources and resume referrals. By combining our resources we are able to recruit all over the country to provide qualified scientific personnel to meet our User Fee and non-User Fee goals. Resumix, an integrated automated, state-of-the-art electronic applicant tracking system for the complex processing and referral of resumes is operational.

The mission of the Equal Employment Opportunity Staff is to plan, develop and administer the Center's Affirmative Employment Program (AEP) and informal complaint process. The Center's AEP includes initiatives and programs designed to increase or expand employment and advancement opportunities for these groups that historically have had limited participation in the workforce. The AEP includes a formal mentoring program, the Biologic Career Path Program, the Administrative Detail Program, targeted recruiting and special emphasis programs. The EEO Staff also sponsors outreach programs to encourage increased representation of minorities in science. The outreach programs include faculty exchange, biotechnology trainee opportunities and structured science based student internships. The EEO Staff provides career counseling services to employees and annual training to CBER through the annual Brown Bag Series of workshops on a variety of EEO-related topics.

The Training and Professional Development Staff (TPDS) directs, manages, coordinates and develops CBER's overall professional and management training program, a formal career development program, a new employee orientation program and related policies.

The TPDS participates as an active member of the CBER Curriculum Committee in the development and implementation of Center-wide scientific and professional training programs. Interaction with the CDER staff college in the development and implementation of scientific and professional training programs is coordinated by TPDS.

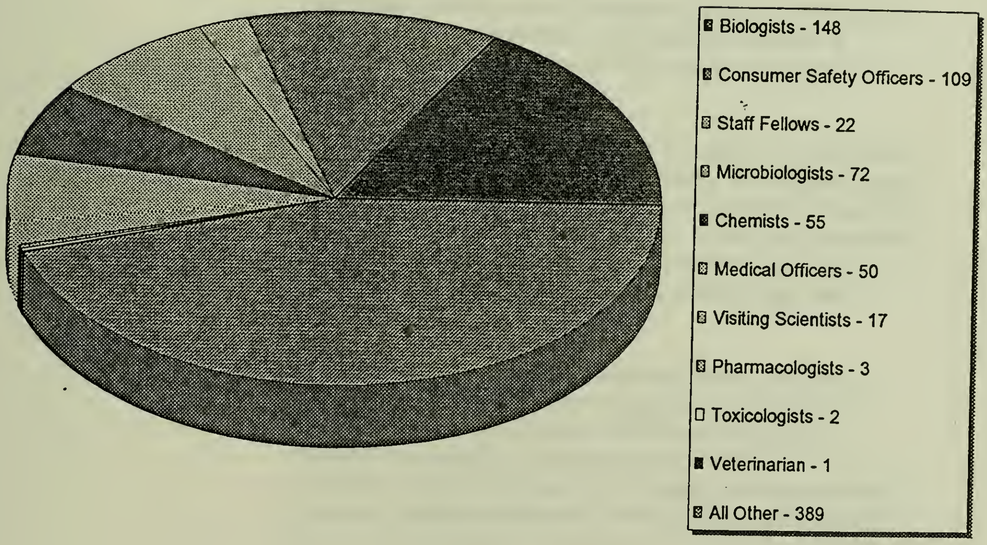
The Safety staff is responsible for maintaining a safe workplace not only for office and laboratory employees, but also for the larger community. Responsibilities include implementing OSHA standards, acquiring appropriate safety certification of laboratory equipment, monitoring compliance with county, state and federal environmental regulations, and managing the portion of building renovations and moves that involve hazardous materials.

RESOURCES

FISCAL YEAR BUDGET

	FY 94 ($000)	FY 95 ($000)
TOTAL CBER BUDGET	**107,436**	**106,931**
PERSONNEL COMPENSATION AND BENEFITS	50,683	56,116
FACILITIES & CENTRALLY FUNDED SUPPORT	16,584	18,844
OPERATING ALLOTMENT	40,169	34,971
INTERAGENCY EXPENDITURES	(638)	(207)
ONE-TIME INCREASES:		
PDUFA Funding	5,665	10,928
Vaccine Funding	9,406	
Blood Reprogramming Funds	1,400	
FDA Women's Issue Funding:		
AIDS	200	
Silicone	170	
Anti-Viral		20
Mucosal Immunity		59
Genital Herpes		128
Arthritis/Lupus		100
Lupus		100
WHO Grant		50
Base Increase for 5 Tissue Banking FTEs	45	
BASE ALLOTMENT	23,921	23,793
TOTAL FTEs USED (Paid Staff Years)	804	808

CBER EMPLOYEES
SCIENTIFIC SERIES
as of end of FY 95



APPENDIX

MEETINGS
WORKSHOPS
SEMINARS

In conjunction with the Recombinant DNA Advisory Committee of the NIH a public meeting on "Somatic Cell and Gene Therapy Production Issues" was held. The meeting was specifically concerned with gene vector and cell transduction facility design. A representative from the Office of Establishment Licensing and Product Surveillance (OELPS) presented a talk, "Facility Design Recommendations for Manufacturers of Early Clinical Trial Gene and Cellular Therapy Products." A number of academic centers have asked CBER for guidance in the planning and building of such facilities.

The Advisory Committee on Biological Response Modifiers met twice to clarify issues related to the safety and efficacy of hematopoietic support regimens in the setting of myelotoxic chemotherapy.

A workshop on Leukoreduced Blood Products was conducted to obtain input from the biomedical community on standards, quality control, and other aspects of blood products that are subjected to procedures to reduce leukocyte content. Those procedures have been associated with an array of favorable results and it is anticipated that blood establishments will increasingly seek licensure for such products.

The Blood Products Advisory Committee met to review and evaluate data on the safety and effectiveness, and on the appropriate use, of blood products intended for use in the diagnosis, prevention, or treatment of human diseases. The committee discussed warnings in the labeling for blood products regarding potential transmission of viral agents, the format for blood container labeling, and the pool size for the manufacture of plasma products.

CBER participated with the National Heart, Lung, and Blood Institute and the U. S. Army in a fibrin sealants workshop. Fibrin sealants are biologic products that contain fibrinogen, thrombin, and other coagulant materials that are applied to wounds to hasten

hemostasis and adhesion. Although such products have been used in the practice of medicine for some time, there has been no formal approval in the United States or Britain, primarily because of the difficulty of demonstrating efficacy.

CBER explained the requirements for clinical studies that would support a claim for true clinical benefit. Specific areas in which such studies might be done were presented and discussed. The workshop attracted representatives from many countries and allowed a full exchange of ideas.

The Human Tissue Program in the Office of Blood Research and Review conducted a workshop on Human Tissue Intended for Transplantation and Human Reproductive Tissue. A document on screening and testing of human tissue was discussed. It will be the core of a guidance document on the testing and screening of tissue donors for high-risk behaviors and for symptoms of human immunodeficiency virus and hepatitis. The workshop was the third in a series. The workshop objectives were: to promote an understanding of related public health issues based on scientific knowledge; to provide an opportunity for discussion of current donor screening and testing practices for reproductive tissue and tissue for transplantation; to identify the practices and procedures of the procurers, processors, distributors, and users of tissue for transplantation and reproductive tissues and their interactions; and, to examine existing state and industry approaches to regulation of tissue for transplantation and reproductive tissue.

Significant issues in the field of xenotransplantation - the transplantation of animal organs and cells into human patients - were addressed at the FDA Biological Response Modifiers Advisory Committee meeting. At a meeting held in July, 1995, the draft guideline, “PHS Considerations in Xenotransplantation,” was developed by FDA/CBER, CDC, NIH, Health Resources and Services Administration (HRSA), the Department of Defense (DoD), and the Department of Agriculture (USDA). The committee agreed that the guidelines should be finalized and published in light of the public health concerns raised by xenotransplantation, and the possibility of inadvertent cross species transmission of infectious agents, primarily viruses, with potential introduction of novel viruses into the transplant recipient and the human population through viral adaptation resulting in altered pathogenicity. The guideline encompasses xenotransplanted cells and tissues, as well as solid organs.

During January, 1995, FDA/CBER conducted a 2-day workshop, "Licensing Blood Establishments." The workshop provided detailed guidance to the blood banking industry on registration and general licensing requirements, the CBER managed review process, establishment license applications, product license applications, changes to be reported, special cases, preapproval programs, and the do's and don'ts of submitting licensing applications.

In June, 1995, CBER co-sponsored the International Scientific Conference on Viral Safety and Evaluation of Viral Clearance from Biopharmaceutical Products. The conference was held in conjunction with a meeting of the ICH Expert Working Group on Quality of Biotechnology Products. The conference brought together international experts from industry, academia and government regulatory agencies to discuss risk assessment related to viral safety for biopharmaceutical products. During the three-day symposium, issues addressed in the context of a wide range of products under the purview of CBER. The products addressed included vaccines, gene therapy, blood and blood products, well-characterized therapeutic products. In addition, there were specific sessions on industry experience with adventitious agents, risk assessment for materials in early clinical trials and cross-Center concerns regarding use of animal derived raw materials and production systems. The open exchange of information during the symposium and subsequent discussions regarding the data presented were instrumental in achieving a harmonized ICH document on viral safety in November, 1995 at ICH3.

ADVERSE EVENTS

The Office of Establishment Licensing and Product Surveillance through the Division of Biostatistics and Epidemiology:

~ participated in the FDA working group to develop new policies regarding the requirements for informed consent in clinical research performed in emergency circumstances as well as a national workshop on this topic;

~ worked with several manufacturers to improve compliance with reporting requirements for adverse experiences by establishing appropriate database systems;

~ participated in manufacturing facility inspection to investigate adverse event reporting practices;

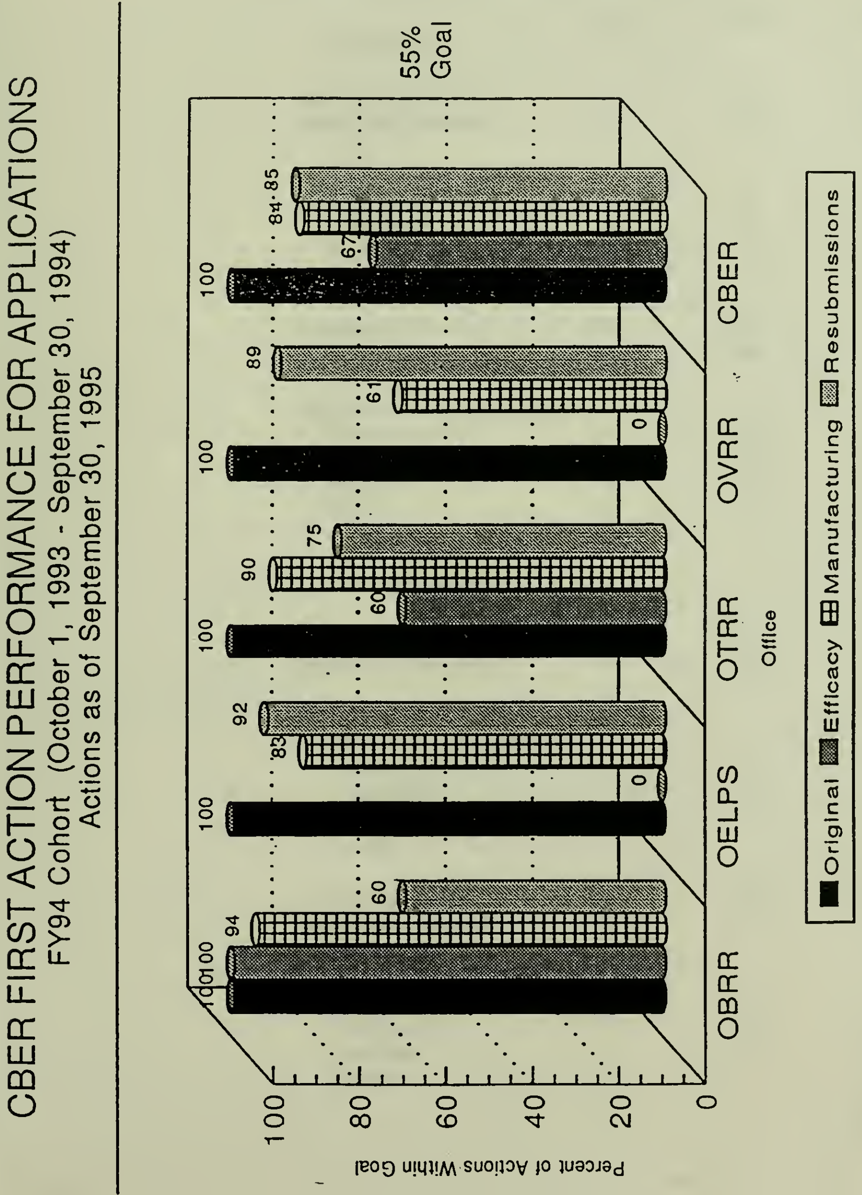
~ began an investigation into the extent to which vaccine adverse events have been evaluated in pre-marketing studies (Exploration of the adequacy of current approaches is being analyzed.);

~ began an investigation into the applicability of neural network methodology to the analysis of vaccine adverse event data (This project is being funded by a grant.);

~ additional methodology was developed with regard to the VAERS database.

CBER FIRST ACTION PERFORMANCE FOR APPLICATIONS - PDUFA

FY 94 COHORT



CBER FIRST ACTION PERFORMANCE FOR APPLICATIONS

FY94 Cohort (October 1, 1993 - September 30, 1994)

Actions as of September 30, 1995

APPLICATION DATA SUMMARY

BIOLOGICAL LICENSING ACTIVITIES

	FY 93	FY 94	FY 95
PRODUCTS			
Applications Received	41	33	52
Applications Approved	31	24	42
Applications (other completions)			
Refusals-To-File	2	8	5
Withdrawals	21	22	10
Inactivated	1	4	1
Denials	-	-	-
Supplements Received	900	720	1386
Supplements Approved	502	536	895
Supplements (other completions)			
Refusals-To-File	2	16	19
Withdrawals	119	104	80
Inactivated	8	15	10
Denials	7	1	0
ESTABLISHMENTS			
Applications Received	11	14	22
Applications Approved	9	10	18
Applications (other completions)			
Refusals-To-File	-	3	2
Withdrawals	8	10	2
Inactivated	-	-	-
Denials	-	-	-
Supplements Received	216	266	392
Supplements Approved	197	251	422
Supplements (other completions)			
Refusals-To-File	1	9	3
Withdrawals	67	24	13
Inactivated	2	1	1
Denials	-	-	-

TOTAL SUBMISSIONS TO CBER

In FY 95, CBER received 57,839 submissions including:

- 3,020 blood establishment registrations
- 536 original INDs and 9,882 IND amendments
- 52 original PLAs and 1,386 PLA supplements
- 22 original ELAs and 392 ELA supplements
- 79 Master Files (590 currently active)
- 52 NDA supplements
- 4 PMAs
- 53 510(k)s
- 1 Orphan Drug application
- 7,256 lots for release
- 20,927 MEDWatch and VAERS adverse event case reports
- 45 hospital fatality reports
- 12,934 Manufacturing Errors and Accident Reports
- 198 export actions and 1,000 requests for Certificates to Foreign Governments

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